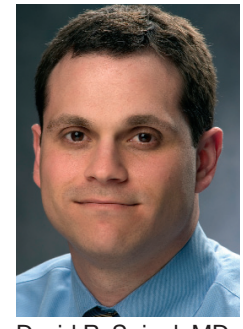
# The Value of Observational Cohort Studies for Cancer Drugs

*Randomized controlled trials — the gold standard for clinical drug evaluation — can't always predict adverse events in real-world settings. For the new cancer therapies, observational cohort studies (OCSs) can help evaluate their effects in broader populations and provide valuable information for future clinical trials.*

**BY DAVID R. SPIGEL, MD**

The gold standard for determining the efficacy and safety of a new cancer therapy is the randomized controlled trial (RCT) (Silverman 2009). Randomization helps balance groups so that differences in outcomes can be attributed to the therapy being tested. RCTs, however, are challenging to conduct because of limited patient and financial resources, time constraints, competing studies, and changing physician and patient interest. Further, when RCTs are completed and produce positive (or negative) results, their findings may be limited in real-world applicability — cancer patients may not always mirror the characteristics of the patient group treated on study because of specific enrollment criteria, study-related procedures, ethical dilemmas, and differences inherent in those patients who chose to participate in the clinical trial. Consequently, how a new drug is used in practice may not always reflect how that drug was used on study, potentially affecting its real-world efficacy and safety profiles. Indeed, a major drawback of RCTs is their inability to definitively evaluate the safety profile of new cancer therapies — the true incidence of drug-related toxicities may not be determined, and newly emergent or rare events may go unreported (Avorn 2007, Ray 2003).

Healthcare payers and providers and pharmaceutical manufacturers, who increasingly rely on the use of evidence-based data to evaluate the effectiveness of innovative therapies relative to current standard-of-care practices, are now looking at additional sources of clinical outcomes data. Such data may come from additional randomized and nonrandomized interventional trials or observational cohort studies (OCSs), any of which may be mandated by the U.S. Food and Drug Administration as a phase 4 post-approval commitment.



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Advances in the understanding of cancer biology have led to the development of multiple new classes of molecular-targeted therapies. Although these therapies have improved survival in select cancers, their long-term benefits and safety profile have not yet been completely defined. Further, the paradigm of combination drug therapy has resulted in an increase in the number of regimens using these agents. Formal and rigorous post-approval study is necessary, therefore, to better characterize these agents and regimens.

## WHAT IS AN OCS?

An OCS is an analysis of a group of individuals who have specific features in common and who are followed over a defined period of time.

Prospective OCSs are designed to examine predefined primary outcomes (Landewé 2007). OCSs are often referred to as registries (Lubeck 2007), although that term is misleading. A registry is a collection of population-based data, including incident events; for example, the Surveillance Epidemiology and End Results (SEER) registry (Lubeck 2007). Generally, a registry does not have prospectively defined outcomes of interest or a finite duration of follow-up and sample size. Analyses of registry data are typically retrospective, whereas OCS data often are prospectively (and retrospectively) analyzed (Landewé 2007). Differences exist among prospective OCSs in terms

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of design and scope. They may compare the outcomes of two cohorts — a treated group and a matched control group. This design is less common among post-approval OCSs where efficacy has already been established in an RCT. Post-approval OCSs generally follow a single cohort, although patient subgroups may be analyzed separately. With respect to scope, many smaller OCSs exist that include patients from restricted populations at single institutions, providing valuable center-specific information. To represent a broad and diverse patient base and to detect rare adverse events, large community-based, multicenter OCSs are useful in the post-approval setting for new therapeutics.

The goal of an OCS is to amass and record key disease- and/or treatment-related data over time for a large heterogeneous patient population treated by a broad base of practitioners (Lubeck 2007). Under that umbrella, an OCS can address specific questions and provide a variety of information that makes these studies valuable and relevant to patients, healthcare providers, and payers alike such as clinical efficacy, safety, survival, health-related quality of life, patient-reported outcomes, resource utilization, cost, clinical practice patterns, and change over time and by geographic region. An OCS also can identify gaps in current clinical trial research and help foster future development of a prospective RCT (Lubeck 2007). Table 1 shows the primary sources of clinical information.

## PROS AND CONS

OCSs have both advantages and disadvantages (Table 2). A major advantage is the ability to collect data that would otherwise be difficult to capture in an RCT, such as rare adverse events, which are often constrained by size and study duration, or might simply be undetectable in a select trial population (Avorn 2007, Ray 2003). For example, neither the randomized trials nor a meta-analysis of those trials revealed the increased risk of myocardial infarction, renal failure, and stroke associated with aprotinin (Trasylol), a pancreatic trypsin inhibitor designed to decrease bleeding during surgery. These rare events were first identified in an observational study that ultimately led to withdrawal of the drug from the market (Mangano 2006, Sedrakyan 2004). Further, patients with uncommon tumor types are not well represented in clinical trials. A large observational study of patterns of care in follicular lymphoma found that only 6 percent of patients

**TABLE 1**
**Primary sources of clinical information**

| Study Type | Description |
|---|---|
| **Randomized Clinical Trials** | Patients are allocated at random to receive one of several clinical interventions. One of the interventions is the standard of comparison or a control (a standard practice, a placebo, or no intervention at all). The process of randomization provides comparable groups for most factors so that differences in outcomes at the conclusion of the trial can be attributed to the intervention being tested. |
| **Nonrandomized Clinical Trials** | Patients are not randomized to treatment. Study participants may choose their treatment group or may be assigned to the groups by the investigators. These are often phase 1 or 2 trials that may include a single treatment arm (no comparator), have small patient populations, and determine more easily assessable endpoints (e.g., response rates, progression-free survival). |
| **Observational Studies** | Observational Cohort Study (OCS): Subjects are classified on the basis of the presence or absence of exposure to a particular factor and then followed for a specified period of time to determine the development of disease in each exposure group.<br><br>Case-control study: A case group of a series of patients who have cancer and a control, or comparison, group of individuals without cancer are selected for investigation, and the proportions with the exposure of interest in each group are compared. (e.g. look at patients with lung cancer and those without, and compare smoking between them). |
| **Patient Registries** | A cancer patient register is designed to collect such information as the occurrence (incidence) of cancer, the types of cancers that occur and their locations within the body, the extent of cancer at the time of diagnosis (disease stage), and the kinds of treatment patients receive and related outcomes. |
| **Post-marketing Commitment Studies** | FDA-required and manufacturer agreed-upon post-marketing commitment studies for drugs and biologics. |

SOURCE: Author Analysis

were treated as part of a clinical trial (Friedberg 2009). Additionally, older patients and patients with a poor performance status or comorbidities are frequently underrepresented in RCTs (Gridelli 2004, Kemeny 2003, Lewis 2003, Muss 2009). OCSs help fill these knowledge gaps and provide additional disease and treatment management data.

Perhaps the most important advantage of OCSs is their utility in helping to characterize drug safety. Recently, there have been a number of post-marketing reports of excess toxicity leading to adverse outcomes for patients and, ultimately, the withdrawal of medications from the market, including tegaserod (Zelnorm), valdecoxib (Bextra), rofecoxib (Vioxx), cerivastatin (Baycol), troglitazone (Rezulin), and efalizumab (Raptiva) among others (Avorn 2006, FDA 2009, Genentech 2009, Topol 2004). As of March 2007, safety-based withdrawals represented approximately 3.5 percent of new molecular entities approved since 1971 (FDA 2009). The FDA assumes responsibility for the post-marketing safety of agents for companies that have not completed mandated Phase 4 trials, which has been an emerging problem in oncology where drugs are commonly 'fast tracked' for approval with a contingency for a follow-up phase 4 study. FDA resources to monitor agents, once approved, also are limited (Brower 2007, Greener 2005). The most recent data show that 70 percent of FDA-mandated post-marketing commitment trials are pending (no patient enrolled or animal dosed) or delayed (DHHS 2008). Furthermore, the FDA mandates very few large observational studies designed to assess safety, and, outside of manufacturer-initiated studies, relies largely on sporadic voluntary reports from patients and providers and independent case reports or small case reports for safety reporting (Avorn 2006, Greener 2005). Case reports are useful to detect events that are distinctive or have a close temporal relationship with medication use, but ultimately are limited by definition to one or at most a few patients, reflecting an almost anecdotal experience (Ray 2003).

The primary disadvantages of OCSs are potential biases inherent in the OCS design and any biases associated with pharmaceutical industry sponsorship. Patient selection (e.g., lack of randomization or unintentional inclusion or exclusion of particular patients); patient attrition (e.g., certain patients may be more likely to drop out); and treatment selection (e.g., a poor prognosis patient may be more likely to receive aggressive therapy than if on a clinical trial) are some biases. Accurately accounting for biases associated with attrition and treatment selection is both possible and

**TABLE 2**
**Advantages and disadvantages of observational cohort studies**

| Advantages | Disadvantages |
|---|---|
| Data on the "real world" use of the drug/intervention in oncology practices. | Data controlled by parties who developed the registry, whether it be public (local, state, federal government, academic institutions), or private (manufacturer, academic, etc.) institutions. |
| Data on the safety of the drug/intervention (e.g., long-term safety use, newly emergent events, and rare adverse events). | Patients are not prospectively randomized to an intervention. Multivariate analyses can help adjust for variables, but cannot exclude unknown factors that would be addressed by a larger randomized analysis. |
| Reflect the patient population treated in a practice setting, beyond the confines of the inclusion and exclusion criteria utilized by RCTs. | Risk of bias is greater: treatment and patient selection, patient attrition. |
| Measure outcomes (survival, etc) in cancers with a long indolent course of disease that may not be captured by RCTs. | |
| Additional measures such as treatment practices (diagnosis, stage of intervention, use of treatment guidelines) in the community setting. | |

RCT=Randomized controlled trial
Source: Author Analysis

important, whereas accounting for selection bias is not statistically feasible (Giordano 2008, Landewé 2007). Utilizing newer and more robust statistical methodologies may improve the results obtained from OCSs, and patient selection and data handling methods are currently evolving (Avorn 2007, Benson 2000, Landewé 2007).

Large OCSs, particularly those evaluating a specific drug, often are sponsored by the drug manufacturers, because of the high costs inherent in conducting these studies. With few exceptions, these studies are conducted voluntarily. However, pharmaceutical company sponsorship is a weakness of OCSs due to the possible introduction of further bias and concerns surrounding the lack of transparency (Avorn 2006, Hiatt 2006). The inherent concern is that the sponsor cannot be objective and will only report favorable outcomes while suppressing negative results (Hermann 2008). One approach to help mitigate this potential bias is to engage independent researchers on OCS steering committees and to make data available to participating investigators for additional analyses (Avorn 2007). Despite these drawbacks, an important consideration is that few OCSs would ever be conducted without a pharmaceutical sponsor. Ultimately, efforts to improve transparency in terms of the study protocol, conduct, and data analysis should be expected and encouraged by the sponsors of these studies.

## OCSs AND CANCER DRUGS

The use of OCSs for evaluating drugs is not unique to oncology. An early example of an OCS was a study of antinausea drugs given in pregnancy that were examined for teratogenicity (Miklovich 1976). Recently, large studies have evaluated biologic agents.

One of the largest studies, the National Registry of Myocardial Infarction, evaluated over 2 million patients suffering acute myocardial infarctions, including over 900,000 patients eligible for reperfusion with either fibrinolytic agents (such as streptokinase, alteplase (Activase), reteplase (Retavase), or tenecteplase (TNKase) or primary percutaneous coronary intervention (Gibson 2008). The results of this study have been used to develop practice guidelines and evaluate the real-world applicability of those guidelines. Antitumor necrosis factor agents for rheumatoid arthritis (RA) have also been studied in large observational trials, a setting that mirrors the current situation in oncology (Gibofsky 2006, Zink 2005). With the approvals of biologics for RA, the need arose for long-term efficacy and safety data in a broad population receiving various nonbiologic concomitant therapies typically used in practice. This information was of particular interest, because these agents are chronic therapies, and in practice, patients received a number of different therapies in various sequences. Patients with RA receive different multidrug regimens with varying sequences according to clinical factors, varying prescribing patterns, and patient wishes. Capturing the efficacy and safety of a new agent in this milieu is not possible with an RCT but is necessary to fully characterize the potential benefits as well as harms.

Because patients are surviving longer with cancer, and targeted agents often have different tolerability profiles than the traditional cytotoxic agents, patients may take anti-cancer therapies chronically for several months or years rather than weeks or a few months. A critical need exists, therefore, for large, well-conducted OCSs for the post-approval evaluation of cancer drugs.

## OCSs IN ONCOLOGY

A selection of ongoing OCSs in oncology is shown in Table 3. Most of the studies have included or plan to include large numbers of patients, providing robust datasets for analyses and can be categorized as one of two types: drug-specific outcomes (e.g., GIDEON, ARIES, and TRUST) or cancer-specific information and practices (e.g., reGIStry, National LymphoCare Study, and registHER). Several of these OCSs are evaluating therapies used to treat some of the most prevalent cancers, including non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and breast cancers.

**Drug-specific OCSs.** One example of a large ongoing, multicenter drug-specific OCS is the Avastin (bevacizumab) Regimens: Investigation of Treatment Effects and Safety (ARIES) study. ARIES is enrolling patients who have received bevacizumab for either NSCLC or CRC at 248 sites in the United States —primarily community oncology clinics. Patients are eligible if they have metastatic or locally advanced CRC or NSCLC and were receiving bevacizumab for less than 3 months in combination with first-line chemotherapy for either indication or as second-line therapy for metastatic CRC. The planned sample size is 4,000 patients, with 2,000 patients for each tumor type. No assessments or treatments are specified by the protocol, and data are collected at baseline and then quarterly, including targeted safety events. The goal of this study is to further delineate the clinical outcomes associated with bevacizumab

use in the practice setting. Bevacizumab, first approved in 2004 for the treatment of metastatic CRC, has been subsequently approved for metastatic breast cancer, advanced NSCLC, glioblastoma, and renal cell carcinoma. Other clinical investigational studies of multiple tumor types are underway, including phase 3 trials in ovarian and prostate cancers and lymphoma, among others.

Bevacizumab is the first and only antivascular endothelial growth factor monoclonal antibody approved as therapy, and complete characterization of the safety of this widely utilized therapy is warranted. Adverse events have been observed with bevacizumab in clinical trials, including severe hypertension, gas-

**TABLE 3**
**Selected ongoing observational cohort studies in oncology**

| Drug/Setting | Study name | Start date | Estimated enrollment | Study description/Purpose | Reference |
|---|---|---|---|---|---|
| Pemetrexed | H3E-US-B001 | 2007 | 1,000 | Ethnic impact of patients undergoing second-line treatment with pemtrexed for non-small cell lung cancer (NSCLC). | NIH 2009 |
| Sunitinib | — | 2008 | 3,000 | Safety and efficacy of sunitinib in patients with gastrointestinal stromal tumors (GIST) or renal cell carcinoma. | NIH 2009 |
| Sunitinib | SUNIKA | 2007 | 600 | Quality of life, safety, efficacy, and tolerability of sunitinib. | NIH 2009 |
| Sorafenib | GIDEON | 2009 | 3,000 | Global study of safety, efficacy, practice patterns, and patient factors associated with sorafenib treatment of hepatocellular carcinoma (HCC). | NIH 2009 |
| Sorafenib | INSIGHT | 2008 | 800 | Efficacy and safety of sorafenib treatment under daily life treatment conditions in patients with HCC. | NIH 2009 |
| Erlotinib | TRUST | 2004 | 7,043 | Global study of the efficacy and safety of erlotinib in patients with stage IIIB/IV NSCLC who had failed on or were unsuitable for chemo-radiotherapy | Groen 2008 |
| Anastrozole | RADAR IIE | 2007 | 1,510 | Quality of life associated with anastrozole in postmenopausal patients with breast cancer. | NIH 2009 |
| Goserelin | AZTEK EXT | 2007 | 1,973 | Quality of life associated with goserelin in patients with prostate cancer. | NIH 2009 |
| Tamoxifen and AIs | TAMARA | 2008 | 1,000 | Quality of life and safety in patients switching from tamoxifen to an aromatase inhibitor therapy. | NIH 2009 |
| Bevacizumab | BRiTE | 2004 | 2,000 | Safety and efficacy in patients with metastatic colorectal cancer (mCRC) receiving bevacizumab and first-line chemotherapy. Choice of chemotherapy is at the physician's discretion. | Grothey 2008, Kozloff 2008, Purdie 2008 |
| Bevacizumab | ARIES | 2006 | 4,000 | Clinical effectiveness of bevacizumab in patients with untreated and relapsed mCRC and untreated NSCLC. | Bekaii-Saab 2008, Fischbach 2009, Lynch 2008 |
| Bevacizumab | VIRGO | 2008 | 2,000 | Treatment patterns and safety outcomes for patients with HER2-normal and hormone receptor-positive metastatic or locally recurrent breast cancer. | NIH 2009 |
| Follicular Lymphoma | National LymphoCare Study | 2004 | 2,728 | Collect information on diagnosis, treatment, and outcomes for patients with newly-diagnosed follicular lymphoma in the United States. | Friedberg 2009, Link 2007 |
| HER2 + Metastatic Breast Cancer | registHER | 2003 | 1,023 | Natural history, treatment patterns, and outcomes in 1,000 newly-diagnosed patients with HER2-positive metastatic breast cancer. | Rugo 2008, Tanchiu 2005 |
| Gastrointestinal Stromal Tumors | reGISTry | 2004 | 1,800 | Internet-based database designed to characterize evolving community and university-delivered patterns of care for non-study patients with GIST. | Blanke 2008, NIH 2009 |

SOURCE: Author Analysis

trointestinal perforations, arterial thromboembolic events, and proteinuria (Hurwitz 2004). OCSs, such as ARIES, have been developed to monitor the occurrence of these events in the general practice setting.

An analysis of 621 patients with NSCLC enrolled in ARIES indicated that the OCS included patients who would have been excluded from the pivotal phase 3 trial, specifically patients with poor performance status, brain metastases, and those receiving therapeutic anticoagulation (Lynch 2008, Sandler 2006). In the CRC patient cohort, ARIES will monitor the use of bevacizumab in patients who received the agent as both first- and second-line therapy (currently 82 [6.75 percent] of 1,214 reported patients) (Bekaii-Saab 2008). Similarly, ARIES will collect data on patients with poor performance status (ECOG PS >2) that were excluded from the phase III RCT in first-line CRC (Bekaii-Saab 2008, Hurwitz 2004).

Preliminary results from ARIES further indicate the utility of a large OCS for characterizing safety in a less selected population (Kozloff 2008, Lynch 2008). Among patients with NSCLC, each serious bevacizumab-related safety event occurred with an incidence of 1 percent or less in a patient population at higher risk for such adverse events due to the broader population studied (Lynch 2008). Similarly, low rates of serious events were observed in the CRC cohort (Bekaii-Saab 2008). Additionally, no new serious adverse events were reported in either cohort.

The Bevacizumab Regimens: Investigation of Treatment Effects and Safety (BriTE) OCS, investigating the use of first-line bevacizumab for metastatic CRC, has included patients 80 years and older, 161 (8.2 percent) of 1,953 patients (Kozloff 2008). This population is underrepresented in clinical trials, and preliminary results from BRiTE have indicated that these patients benefit from bevacizumab (Balducci 2007, Kozloff 2008). An ongoing representative cancer-specific OCS is the SISTER study, which will follow approximately 50,000 sisters of women who have had breast cancer and will prospectively examine environmental and familial risk factors for breast cancer and other diseases (NIH 2009).

OCSs also may focus on health-related quality of life associated with a specific type of cancer, such as the Memorial Sloan Kettering Cancer Center study of approximately 1,800 men with localized prostate cancer (NIH 2009). The National LymphoCare Study is collecting information on nearly 3,000 patients with follicular lymphoma, 80 percent of whom are treated at nonacademic sites, and is providing important insights into current treatment practices for this condition. Early analysis has revealed that physician practices differ from current guideline recommendations; specifically, among patients with Stage I/II disease, only about 30 percent of patients received initial treatment with radiotherapy and nearly 30 percent received no initial therapy (observation alone) despite the potential curability of follicular lymphoma at this stage. This study also will provide a valuable foundation on which to build future clinical trials (Friedberg 2009).

## VALUE IN THE REAL WORLD

The development of targeted therapies represents a shift in the treatment paradigm for cancer. As survival continues to improve with advances in treatment, patients may receive long-term therapy; therefore, it is imperative to have a complete and thorough understanding of the safety and effectiveness of these drugs in the community practice. Clinical cancer studies are primarily designed to evaluate the efficacy of the agents within the confines of the trial construct, and it is not until post-approval use in larger numbers of patients that rare, but serious, drug-related events may emerge. Anecdotal case reporting of such events, while serving an important role in their recognition, is an insufficient method of determination. Prospective OCSs can provide valuable clinical information about the safety and effectiveness of cancer therapies and represent an additional source of clinical information that complements RCTs and other types of studies.

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## Disclosure

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